



(43) International Publication Date 9 October 2003 (09.10.2003)

PCT

(10) International Publication Number WO 03/082862 A1

(51) International Patent Classification⁷: C07D 413/12, 413/14, 417/14, 265/30, C07C 215/10, A61K 31/5377, A61P 29/00

(21) International Application Number: PCT/EP03/03347

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 0208158.6

28 March 2002 (28.03.2002) GB

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ANCLIFF, Rachael, Ann [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COOK, Caroline, Mary [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ELDRED, Colin, David [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GORE, Paul, Martin [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HARRISON, Lee, Andrew [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HAYES, Martin, Alistair [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HODGSON, Simon, Teanby [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDD, Duncan, Bruce [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). KEELING, Suzanne, Elaine [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). LEWELL, Xiao, Qing [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MILLS, Gail [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ROBERTSON, Graeme, Michael [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SWANSON, Stephen [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WALKER, Andrew, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WILKINSON, Mark [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

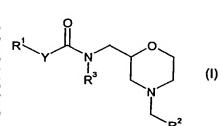
Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTI-INFLAMMATORY MORPHOLIN-ACETAMIDE DERIVATIVES

WO 03/082862



(57) Abstract: Certain compounds of formula (I): wherein: R^1 represents substituted or unsubstituted heteroaryl; Y represents -($CR_{n_B}R_{n_b}$)_n-; R_{n_B} and R_{n_b} are each independently hydrogen or C_{1-6} alkyl; n is an integer from 1 to 5; R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl; R^3 represents hydrogen or C_{1-6} alkyl; and salts and solvates thereof are CCR-3 antagonists and are thus indicated to be useful in therapy.



Intel Conal Application No PCT/EP 03/03347

A. CLASSIFICATION OF SUBJECT MATTER 1PC 7 C07D413/12 C07D413/14 C07D417/14 C07D265/30 C07C215/10 A61K31/5377 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

Category *	Citation of document, with indication, where appropriate, of	Relevant to claim No.	
Jaicgory	Oldanori di document, vini in dice e propini di		
A	WO 00 71518 A (SEPRACOR INC) 30 November 2000 (2000-11-30) claims	1-22	
A	EP 0 243 959 A (DAINIPPON PHA CO) 4 November 1987 (1987-11- claims	1-22	
	·	-/	
			1
X Furt	her documents are listed in the continuation of box C.	X Patent family members ar	e listed in annex.
<u> </u>	ther documents are listed in the continuation of box C.	"T' later document published after	the International filing date
Special ca	stegories of cited documents :	"T" later document published after to repriority date and not in conficied to understand the princip	the international filling date lict with the application but
Special ca	stegories of cited documents : ent defining the general state of the art which is not dered to be of particular relevance	*T' later document published after or priority date and not in cont cited to understand the princip invention *X' document of particular relevance.	the international filing date lict with the application but ale or theory underlying the be: the claimed invention
A docum consider *E* earlier	stegories of cited documents : ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date	*T' later document published after or priority date and not in conficied to understand the princip invention *X' document of particular relevant cannot be considered novel of	the international filing date lict with the application but ale or theory underlying the be: the claimed invention
* Special ca *A* documents on slot of the cartier filing of the country which	ent defining the general state of the art which is not defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date on twich may throw doubts on priority claim(s) or is cited to establish the publication date of another	*T' later document published after or priority date and not in conficied to understand the princip invention *X' document of particular relevant cannot be considered novel of involve an inventive step when the company of particular relevant of particular relevant to particular to particular particular particular particular particular particu	the international filing date lict with the application but alle or theory underlying the be; the claimed invention cannot be considered to the document is taken alone be; the claimed invention
Special ca 'A' docume consider 'E' earlier filing of the county which citation 'O' docume 'O' docume	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority clalm(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or	"T" later document published after or priority date and not in conficied to understand the princip invention "X" document of particular relevant cannot be considered novel or involve an inventive step where "Y" document of particular relevant cannot be considered to involve document is combined with or	the international filing date lict with the application but alle or theory underlying the be; the claimed invention cannot be considered to the document is taken alone be; the claimed invention we an inventive step when the e or more other such docu-
° Special ca °A° docum conside °E° earlier filing of clatica °O° docum other °P° docum	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but	*T' later document published after or priority date and not in conficied to understand the princip invention *X' document of particular relevant cannot be considered novel of involve an inventive step where the cannot be considered to involve document of particular relevant cannot be considered to involve document is combined with or ments, such combination bein in the art.	the international filing date lict with the application but one or theory underlying the ca; the claimed invention cannot be considered to the document is taken alone to the document is taken alone to the claimed invention we an inventive step when the er or more other such docug g obvious to a person skilled
"A" docum consider filing of the citation of t	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ant which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but han the priority date claimed	"T" later document published after or priority date and not in conficied to understand the princip invention "X" document of particular relevant cannot be considered novel of involve an inventive step where cannot be considered to involve document is combined with or ments, such combination bein in the art.	the international filing date lict with the application but application but all or theory underlying the ce; the claimed invention reannot be considered to the document is taken alone to the document invention we an inventive step when the error more other such docugo by patent family
A docum consider filing of the citation of t	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but	*T' later document published after or priority date and not in conficied to understand the princip invention *X' document of particular relevant cannot be considered novel of involve an inventive step where the cannot be considered to involve document of particular relevant cannot be considered to involve document is combined with or ments, such combination bein in the art.	the international filing date lict with the application but application but all or theory underlying the ce; the claimed invention reannot be considered to the document is taken alone to the document invention we an inventive step when the error more other such docugo by patent family
Special call of the construction of the cartier of the call of the	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ant which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but han the priority date claimed	"T" later document published after or priority date and not in conficied to understand the princip invention "X" document of particular relevant cannot be considered novel of involve an inventive step where cannot be considered to involve document is combined with or ments, such combination bein in the art.	the international filing date lict with the application but application but all or theory underlying the ce; the claimed invention reannot be considered to the document is taken alone to the document invention we an inventive step when the error more other such docugo by patent family
Special ca 'A' docume consider to docume which citatio 'O' docume other 'P' docume tater to Date of the	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but han the priority date claimed actual completion of the international search 7 July 2003 mailing address of the ISA	*T' later document published after or priority date and not in conficied to understand the princip invention *X' document of particular relevant cannot be considered novel of involve an inventive step where cannot be considered to involve document of particular relevant cannot be considered to involve document is combined with or ments, such combination being in the art. *&* document member of the same	the international filing date lict with the application but application but all or theory underlying the ce; the claimed invention reannot be considered to the document is taken alone to the document invention we an inventive step when the error more other such docugo by patent family
Special ca 'A' docume consider 'E' earlier filing of the citation other 'P' docume tater to the citation of the citation of the citation of the citation other citation of the citation of th	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ant which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filling date but han the priority date claimed actual completion of the international search	"T" later document published after or priority date and not in conficied to understand the princip invention "X" document of particular relevant cannot be considered novel of involve an inventive step where "y" document of particular relevant cannot be considered to involve document is combined with or ments, such combination bein in the art. "&" document member of the same Date of mailting of the internation."	the international filing date lict with the application but application but all or theory underlying the ce; the claimed invention reannot be considered to the document is taken alone to the document invention we an inventive step when the error more other such docugo by patent family



. . . . 3

i	Interior	pplication No
	PCT/EP	03/03347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
	citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Category °	Cuation of document, with management, where appropriate, of the feature, passages	
A	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTROKINETIC AGENTS 2. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 4-AMINO-5-CHLORO-2-ETHOXY-N-4-(4-FLUOROBEN ZYL)-2-MORPHOLINYL METHYLBENZAMIDE CITRATE (AS-4370) AND RELATED COMPOUNDS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 2, February 1991 (1991-02), pages 616-624, XP001037842 ISSN: 0022-2623 the whole document	1-22
P,A	WO 02 26722 A (HARRISON LEE ANDREW; JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) claims	1-22



1 >



Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	rnational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Although claims 16, 18 are directed to a method of treatment of
	the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
· ا	restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.
	No protest accompanies the payment of adminima section ress.



 $\nu \in \mathcal{Y}$

Information on patent family members

Internal Application No PCT/EP 03/03347

Patent document dted in search report		Publication date		Patent family member(s)	Publication date
WO 0071518		30-11-2000	AU	5295300 A	12-12-2000
			CA	2372887 A1	30-11-2000
			EP	1187810 A2	20-03-2002
			JP	2003500392 T	07-01-2003
			WO	0071518 A2	30-11-2000
			US	2003069418 A1	10-04-2003
EP 0243959	Α	04-11-1987	AT	79616 T	15-09-1992
C. 02.0505			AU	592177 B2	04-01-1990
			AU	7227587 A	05-11 - 1987
		•	CA	1291135 C	22-10-1991
			CZ	8702897 A3	11-11-1998
			DD	256325 A5	04-05-1988
			DE	3781195 D1	24-09-1992
			DE	3781195 T2	18-02-1993
			DK	218787 A	31-10-1987
			EP	0243959 A1	04-11-1987
			ES	2043617 T3	01-01-1994
			FI	871828 A ,E	31-10-1987
			GR	3005934 T3	07-06-1993
			HK	18194 A	11-03-1994
			HU	45514 A2	28-07-1988
			HU	198193 B	28-08-1989
			JP	1686407 C	11-08-1992
			JP	3054937 B	21-08-1991
			JP	63264467 A	01-11-1988
			JP	2042069 A	13-02-1990
			MX	6263 A	01-11-1993
			NZ	220120 A	28-06-1989
			PH	24049 A	05-03-1990
			SG	494 G	15-04-1994
,			SK	289787 A3	03-06-1998
			SU	1597101 A3	30-09-1990
			US	4870074 A	26-09-1989
			ZA	8703022 A	20-10-1987
			KR	9508530 B1	31-07-1995
W0 0226722	Α	04-04-2002	AU	9014301 A	08-04-2002
			WO	0226722 A1	04-04-2002
			NO	20031442 A	26-05-2003